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(21) International Application Number: PCT/CA97/00349 (22) International Filing Date: 22 May 1997 (22.05.97) (30) Priority Data: 08/661,329 14 June 1996 (14.06.96) US (71) Applicant: THERATECHNOLOGIES INC. [CA/CA]; Sème Etage, 630 boulevard René-Lévesque Ouest, Montréal, Québec H3B 1S6 (CA). (72) Inventors: BRAZEAU, Paul; 4054 avenue Parc Lafontaine, Montréal, Québec H2L 3M8 (CA). ABRIBAT, Thierry; 3539 de Bordeaux, Montréal, Québec H2K 3Z2 (CA). IBEA, Michel; Apartment 12, 1575 Plessis, Montréal, Québec H2L 2X6 (CA). (74) Agent: COTE, France; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montréal, Québec H3A 2Y3 (CA).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: LONG-ACTING GALENICAL FORMULATION FOR GRF PEPTIDES (57) Abstract <p>The present invention relates to a long-acting galenical formulation of GRF peptides, pro-GRF and/or analogs thereof which comprises about 1 to about 100 mg of a GRF peptide, fragment or analog thereof pressed from about 1 to about 100 kg/mm² in a tablet for parenteral administration, whereby these GRF peptides are released as the tablet is eroded.</p> <p><i>medicines prepared according to formulas of Galen. standard preparations containing 1 or several organic ingredients, as contrasted with pure chemical substances.</i></p>		

one class of
GHs
= GRF or
GHRH

LONG-ACTING GALENICAL FORMULATION FOR GRF PEPTIDES

BACKGROUND OF THE INVENTION

(a) Field of the Invention

5 The invention relates to a long-acting galenical formulation of GRF peptides, pro-GRF and/or GRF analogs having a long-lasting and prolonged activity.

(b) Description of Prior Art

10 Growth hormone (GH) or somatotropin, secreted by the pituitary gland constitute a family of hormones which biological activity is fundamental for the linear growth of a young organism but also for the maintenance of the integrity at its adult state. GH acts directly or indirectly on the peripheral organs by stimulating
15 the synthesis of growth factors (insulin-like growth factor-I or IGF-I) or of their receptors (epidermal growth factor or EGF). The direct action of GH is of the type referred to as anti-insulinic, which favors the lipolysis at the level of adipose tissues. Through
20 its action on IGF-I (somatomedin C) synthesis and secretion, GH stimulate the growth of the cartilage and the bones (structural growth), the protein synthesis and the cellular proliferation in multiple peripheral organs; including muscles and the skin. Through its
25 biological activity, GH participates within adults at the maintenance of a protein anabolism state, and plays a primary role in the tissue regeneration phenomenon after a trauma.

30 The decrease of GH secretion with the age, demonstrated in humans and animals, favors a metabolic shift towards catabolism which initiates or participate to the aging of an organism. The loss in muscle mass, the accumulation of adipose tissues, the bone demineralization, the loss of tissue regeneration capacity
35 after an injury, which are observed in elderly, correlate with the decrease in the secretion of GH.

GH is thus a physiological anabolic agent absolutely necessary for the linear growth of children and which controls the protein metabolism in adults.

The secretion of GH by the pituitary gland is principally controlled by two hypothalamic peptides, somatostatin and growth hormone-releasing factor (GRF). Somatostatin inhibits its secretion, whereas GRF stimulates it.

The human GH has been produced by genetic engineering for about ten years. Until recently most of the uses of GH were concerned with growth delay in children and now the uses of GH in adults are studied. The pharmacological uses of GH and GRF may be classified in the following three major categories.

Children growth

Treatments with recombinant human growth hormone have been shown to stimulate growth in children with pituitary dwarfism, renal insufficiencies, Turner's syndrome and short stature. Recombinant human GH is presently commercialized as an "orphan drug" in Europe and in the United States for children's growth retardation caused by a GH deficiency and for children's renal insufficiencies. The other uses are under clinical trial investigation.

Long term treatment for adults and elderly patients

A decrease in GH secretion causes changes in body composition during aging. Preliminary studies of one-year treatment with recombinant human GH reported an increase in the muscle mass and in the thickness of skin, a decrease in fat mass with a slight increase in bone density in a population of aged patients. With respect to osteoporosis, recent studies suggest that recombinant human GH does not increase bone mineralization but it is suggested that it may prevent bone

demineralization in post-menopausal women. Further studies are currently underway to demonstrate this theory.

5 Short term treatment in adults and elderly patients

In preclinical and clinical studies, growth hormone has been shown to stimulate protein anabolism and healing in cases of burn, AIDS and cancer, in wound and bone healing.

10 GH and GRF are also intended for veterinary pharmacological uses. Both GH and GRF stimulate growth in pigs during its fattening period by favoring the deposition of muscle tissues instead of adipose tissues and increase milk production in cows, and this without
15 any undesired side effects which would endanger the health of the animals and without any residue in the meat or milk being produced. The bovine somatotropin (BST) is presently commercialized in the United States.

Most of the clinical studies presently undertaken were conducted with recombinant GH. The GRF is considered as a second generation product destined to replace in the near future the uses of GH in most instances. Accordingly, the use of GRF presents a number of advantages over the use of GH *per se*.

25

Physiological advantages

Growth hormone (GH) is secreted by the pituitary gland in a pulse fashion, since this rhythm of secretion is crucial for an optimal biological activity. The administration of GH to correspond to its natural mode of secretion is difficult to achieve.
30 When GRF is administered in a continuous fashion as a slow releasing preparation or as an infusion, it increases GH secretion while respecting its pulsatility.
35

The recombinant GH which is presently commercialized is the 22 kDa form whereas GRF induces the synthesis and secretion from the pituitary gland of all the chemical isomers of GH which participate in a wider
5 range of biological activities.

A treatment with GH results in a decreased capacity of the pituitary gland to secrete endogenous growth hormone, and the GH response to GRF is diminished after such a treatment. On the contrary, a
10 treatment with GRF does not present this disadvantages, its trophic action on the pituitary gland increases this gland secreting capacity in normal animals and in patients with somatotroph insufficiency.

15 **Economical advantages**

The production of GH by genetic engineering is very expensive for clinical use. In particular, there are risks of contamination of these commercial preparation with material from the bacterial strain used.
20 These bacterial contaminants may be pyrogens or may result in immunogenic reactions in patients. The purification of the recombinant product is effected by following a plurality of successive chromatography steps. The drastic purity criteria causes multiple quality
25 control steps.

The synthesis of GRF is of chemical nature. The synthesis effected in a solid phase and its purification is carried out in a single step using high performance liquid chromatography (HPLC). Also the quantity of GRF to be administered is much less than the
30 quantity of GH for the same resulting biological activity.

Even with all these advantages, GRF is still not commercialized to date as a therapeutic agent mainly
35 because of its chemical instability. The human GRF is a peptide of 44 amino acids of the following sequence:

Tyr Ala Asp Ala Ile Phe Thr Asn Ser Tyr Arg Lys Val Leu Gly Gln
1 5 10 15

5 Leu Ser Ala Arg Lys Leu Leu Gln Asp Ile Met Ser Arg Gln Gly
20 25 30

Glu Ser Asn Gln Glu Arg Gly Ala Arg Ala Arg Leu-NH₂
35 40 (SEQ ID NO:1).

The minimum active core is hGRF (1-29)NH₂

10 Tyr Ala Asp Ala Ile Phe Thr Asn Ser Tyr Arg Lys Val Leu Gly Gln
1 5 10 15

Leu Ser Ala Arg Lys Leu Leu Gln Asp Ile Met Ser Arg
20 25 (SEQ ID NO:2).

15 Clinical studies with children and adults have confirmed that natural hGRF (1-44)NH₂ or the active fragment hGRF (1-29)NH₂ are not potent enough to produce equal effects corresponding to those of recombinant GH.

20 It is now well documented that hGRF has a very short half-life in serum, being rapidly enzymatically cleaved and inactivated following its injection. As a result, numerous studies have reported that hGRF or its analogs have to be injected daily or several times a
25 day in human and animals to effectively exert its anabolic effect through growth hormone and IGF-I releases. This kind of treatment regimen requiring multiple injections is very time consuming and uncomfortable for the patients, which has so far hampered the clinical
30 use of hGRF and analogs.

Several GRF preparations have been described (U.S. Patents Nos. 5,137,669, 5,039,660 and 5,192,741, respectively issued on August 11, 1992, August 13, 1991 and March 9, 1993), in which GRF is mixed with various
35 carriers to increase its duration of action. However, all those preparations incorporate carriers that may induce immune or inflammatory reactions following administration.

Advantage

It would be highly desirable to be provided with a long-acting galenical formulation of GRF peptides, pro-GRF and/or GRF analogs having a long-lasting and prolonged activity without the addition of any carrier.

5

SUMMARY OF THE INVENTION

One aim of the present invention is to provide a long-acting galenical formulation of GRF peptides, pro-GRF and/or GRF analogs having a long-lasting and prolonged activity without the addition of any carrier.

10 In accordance with the present invention there is provided a long-acting galenical formulation of GRF peptides, pro-GRF and/or analogs thereof which comprises about 1 to about 100 mg of a GRF peptide, fragment or analog thereof pressed from about 1 to about 100 kg/mm² in a tablet for parenteral administration, whereby these GRF peptides are released as the tablet is eroded.

20 Any GRF peptides, pro-GRF, fragments or analogs thereof may be used in accordance with the present invention. The nature of the GRF peptide is irrelevant to the present invention, as the essence of the present invention resides in the pressed or tablet formulation of any GRF peptides to slow down their erosion and release in body fluids in order to maximize the effect in time. The teachings of U.S. Patents Nos. 4,517,181, 4,585,756, 4,605,643 and 4,610,976 and U.S. Patent application serial number 08/453,067 and a continuation-in-part application (unavailable number) respectively filed on May 26, 1995 and May 22, 1996 are incorporated herein by reference.

25 The tablet can be pressed from about 1 to about 100 kg/mm², most preferably from about 2 to about 10 kg/mm².

any impact on GH5?

The pressed tablet of the present invention may have a cylindrical shape with a minimal dimension value from about 0.5 mm to about 6 mm. The diameter may be between 0.5 mm to about 6 mm in order to be practically injectable using a needle or trocar for subcutaneous administration to the patient. By using such a gage 20-16 needle, it avoids having to proceed with a local anesthesia prior to the administration of the tablet. The length of the cylindrical tablet can be between 2 mm to about 40 mm. The tablet can be portioned lengthwise to form a plurality of doses in thinner cylinders (in about 2 to 5 parts).

The diameter and/or the length of the tablet as well as the pressure used in its manufacturing can be varied to adjust the chosen releasing speed of the GRF peptides which is proportional to the desired erosion speed of the tablet for a definite dose.

The dosage to be administered to a patient varies from about 4 to about 40 mg of GRF peptides pressed from about 2 to about 10 kg/mm².

DETAILED DESCRIPTION OF THE INVENTION

Surprisingly and in accordance with the present invention, there is provided a long-acting galenical formulation of GRF peptides, pro-GRF and analogs thereof which comprises about 4 to about 100 mg of a GRF peptide, fragment or analog thereof pressed from about 1 to about 100 kg/mm² in a tablet for parenteral administration, whereby the GRF peptide is released as the tablet is eroded in a selected time schedule.

The tablet of the present invention can release GRF peptide for up to at least 14 days.

The preferred tablet of the present invention is pressed at about 6.5 kg/mm².

In accordance with the present invention, pig was selected as a test specie, since it is a valuable preclinical model for the testing of the GRF formulation tablet of the present invention. Indeed, human
5 and porcine GRF(1-29)NH₂ share a 100% homology of structure, and the physiological pattern of GH secretion is almost identical in both species.

Moreover, the potency of the long-acting galenical GRF formulation was assessed as its ability to significantly increase IGF-I blood levels rather than its
10 acute GH releasing potency. Indeed, it is known that the anabolic and healing effects of GH or GRF induced GH are mediated by an increase in IGF-I synthesis and secretion, a more easy and thorough indication of all
15 anabolic effect of an improved GH secretion. Therefore, the measurement of GRF induced IGF-I elevation is the best indicator of the treatment efficacy,

The present invention will be more readily understood by referring to the following examples which
20 are given to illustrate the invention rather than to limit its scope.

EXAMPLE I

Effect of a tablet made of mechanically compressed (Hexenoyl trans-3)₀ hGRF (1-29) NH₂ on IGF-I secretion
25 in pigs

This experiment was conducted to assess the potency of a long-acting GRF preparation, made of compressed (Hexenoyl trans-3)₀ hGRF (1-29) NH₂, without the addition of any other excipient.

30 (Hexenoyl trans-3)₀ hGRF (1-29) NH₂ is a combination of the natural hGRF(1-29)NH₂ and a natural fatty acid, which has already been described in co-pending U.S. Patent application serial number 08/453,067 filed on May 26, 1995.

35

Identity of test articles

- Control
 - A - (Hexenoyl trans-3)₀ hGRF (1-29) NH₂, compression
A, 14 mg at 6.5 kg/mm²
 - 5 B - (Hexenoyl trans-3)₀ hGRF (1-29) NH₂, compression
B, 14 mg at 16.5 kg/mm²
- Both (Hexenoyl trans-3)₀ hGRF (1-29) NH₂ treatments differ by the fact that the tablets are made with a different level of mechanical compression (6.4 vs.
10 16.0 kg/mm²).

Route and frequency of test article administration

Subcutaneous injection of the tablets.

15 Test system

Landrace x Yorkshire pigs.

Animal description

- Twenty-four (24) growing barrows pigs weighing
20 35 kg at the time of purchase.

Ration

- Commercial feed concentrate (18% minimum) protein offered *ad libitum*.
25

Experimental design

- Twenty-four (24) pigs will be randomly distributed into 3 experimental groups (n = 8 pigs/group).
- Group 1 Control
 - 30 Group 2 (Hexenoyl trans-3)₀ hGRF (1-29) NH₂,
14 mg, compressed tablet A
 - Group 3 (Hexenoyl trans-3)₀ hGRF (1-29) NH₂,
14 mg, compressed tablet B
- The tablets were surgically subcutaneously
35 inserted following pig light anesthesia.
- Blood samples for IGF-I measurement were collected daily, from 2 days before to 14 days after tab-

lets implantation and finally at 40 days post-implantation . Blood samples were allowed to clot at +4°C. Serum were harvested by centrifugation, stored at -20°C and assayed for IGF-I.

TABLE 1

	Day 1 (preimplantatio n)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 8	Day 10	Day 12	Day 14	Day 40
Controls	165 ± 15	163 ± 17	158 ± 22	178 ± 22	188 ± 21	197 ± 27	192 ± 28	204 ± 25	186 ± 28	209 ± 27	164 ± 11 (-1)
14 mg GRF(1) Preparation A	214 ± 19	241 ± 14	288 ± 16 ^a	265 ± 16 ^a	274 ± 20 ^a	290 ± 15 ^a	295 ± 14 ^a	296 ± 16 ^a	277 ± 15 ^a	285 ± 19 ^a	192.9 ± 24
14 mg GRF(1) Preparation B	189 ± 28	218 ± 28	236 ± 28 ^a	247 ± 24 ^a	251 ± 29 ^a	264 ± 33 ^a	264 ± 27 ^a	258 ± 27 ^a	263 ± 24 ^a	270 ± 23 ^a	175.3 ± 26

Effect of time (days): $P < 0.0001$ Effect of treatments: $P = 0.011$ Time x Treatments: $P = 0.612$ ^a $P < 0.05$ when compared to day 1(1) synthetic pro-hGRF (1-29)NH₂ N-(hexenoyl trans 3^o) hGRF(1-29)NH₂Preparation A = 6.4 kg/mm² = softPreparation B = 16.0 kg/mm² = hard

The results shown in Table 1 demonstrate that IGF-I levels did not vary significantly over the study period in the control group. In contrast, it is increased over basal values (day 1: pre-implantation), this increase being statistically significant from day 3 to day 14 following implantation of the GRF tablets. The IGF-I increase ranged from 24% to 42% in the group injected with preparation A (14mg GRF; 6.4 kg/mm²) and from 25% to 43% in the group injected with preparation B (14mg GRF; 16.0 kg/mm²) between day 3 and 16 over day 1. No difference was observed between both GRF-treated groups, indicating that both compression intensities tested (6.4 vs. 16.0 kg/mm²) were equally effective in providing a slow releasing formulation for GRF.

Finally, on day 40 following implantation, IGF-I levels were returned to pre-implantation levels in both GRF groups.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION

- (i) APPLICANT: Thératechnologies Inc.
- (ii) TITLE OF THE INVENTION: LONG-ACTING GALENICAL FORMULATION FOR GRF PEPTIDES
- (iii) NUMBER OF SEQUENCES: 2
- (iv) CORRESPONDENCE ADDRESS:
 - (A) ADDRESSEE: SWABEY OGILVY RENAULT
 - (B) STREET: 1981 McGill College Ave. - Suite 1600
 - (C) CITY: Montréal
 - (D) STATE: QC
 - (E) COUNTRY: Canada
 - (F) ZIP: H3A 2Y3
- (v) COMPUTER READABLE FORM:
 - (A) MEDIUM TYPE: Diskette
 - (B) COMPUTER: IBM Compatible
 - (C) OPERATING SYSTEM: DOS
 - (D) SOFTWARE: FastSEQ for Windows Version 2.0
- (vi) CURRENT APPLICATION DATA:
 - (A) APPLICATION NUMBER:
 - (B) FILING DATE:
 - (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:
 - (A) APPLICATION NUMBER: 08/661,329
 - (B) FILING DATE: 14-JUN-1996
- (viii) ATTORNEY/AGENT INFORMATION:
 - (A) NAME: Côté, France
 - (B) REGISTRATION NUMBER: 4166
 - (C) REFERENCE/DOCKET NUMBER: 12411-10PCT
- (ix) TELECOMMUNICATION INFORMATION:
 - (A) TELEPHONE: 514 845-7126
 - (B) TELEFAX: 514 288-8389
 - (C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 44 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Tyr	Ala	Asp	Ala	Ile	Phe	Thr	Asn	Ser	Tyr	Arg	Lys	Val	Leu	Gly	Gln
1				5					10					15	
Leu	Ser	Ala	Arg	Lys	Leu	Leu	Gln	Asp	Ile	Met	Ser	Arg	Gln	Gln	Gly
			20					25					30		
Glu	Ser	Asn	Gln	Glu	Arg	Gly	Ala	Arg	Ala	Arg	Leu				
		35					40								

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 29 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Tyr	Ala	Asp	Ala	Ile	Phe	Thr	Asn	Ser	Tyr	Arg	Lys	Val	Leu	Gly	Gln
1				5					10					15	
Leu	Ser	Ala	Arg	Lys	Leu	Leu	Gln	Asp	Ile	Met	Ser	Arg			
			20					25							

WE CLAIM:

1. A long-acting galenical formulation of GRF peptides, pro-GRF and/or analogs thereof which comprises about 1 to about 100 mg of a GRF peptide, fragment or analog thereof pressed from about 1 to about 100 kg/mm² in a tablet for parenteral administration, whereby these GRF peptides are released as the tablet is eroded.
2. The formulation of claim 1, wherein the tablet is pressed from about 2 to about 10 kg/mm².
3. The formulation of claim 1, wherein the tablet has a cylindrical shape with a diameter between 0.5 mm to about 6 mm and a length between 2 mm to about 40 mm.
4. The formulation of claim 1, wherein the dosage is from about 4 to about 40 mg of GRF peptides.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 97/00349

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K38/25 A61K9/00 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 535 899 A (ELI LILLY) 7 April 1993 see the whole document ---	1-4
A	US 5 137 669 A (R.J.LEONARD ET AL.) 11 August 1992 cited in the application see the whole document ---	1-4
A	US 5 137 872 A (J.E.SEELEY ET AL.) 11 August 1992 see the whole document ---	1-4
A	US 5 192 741 A (P.ORSOLINI ET AL.) 9 March 1993 cited in the application see the whole document ---	1-4
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Z document member of the same patent family

Date of the actual completion of the international search

15 October 1997

Date of mailing of the international search report

22.10.97

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INTERNATIONAL SEARCH REPORT

Intern. J. Application No
PCT/CA 97/00349

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		